An Overview of INHIBITORS

General Information

One of the most serious and costly complications of hemophilia, unfortunately also happens to be one of the most common. This complication, which occurs in as many as 30 percent of patients with hemophilia, is the development of an antibody – an inhibitor – to the product being used to treat or prevent bleeding.

Patients with hemophilia have a reduced level of specific clotting factors, which makes it more difficult for their bodies to form clots when they become injured. Treatment consists of replacing those clotting factors with factor replacement products.

Inhibitors occur when the patient's body recognizes the factor replacement product as a foreign substance that must be destroyed. The patient's immune system then creates inhibitors to attack the foreign substance and this keeps the product from working. Inhibitors usually occur within the first year of treatment, but may occur at any time.

Risk Factors and Causes

Scientists have not yet been able to determine exactly what causes inhibitors to develop. However, studies have pointed out some possible risk factors that may play a role. These include:

Age: First appearance most often in children.

Race/ethnicity: Patients from African descent are more likely than those of other races to develop an inhibitor.

Type of hemophilia gene defect: More Type A (factor VIII deficiency) hemophiliacs are affected (25-30%) than Type B (factor IX deficiency) (1-6%). Additionally, patients with severe disease are more likely to be affected.

Frequency and amount of treatment: Most inhibitors develop within the first 50 exposures to factor, with the greatest risk occurring between the first 10-20 treatments.

Family history of inhibitors: Those with a family history of inhibitors, especially those with a sibling who has an inhibitor, are much more likely to develop an inhibitor.

Type of factor replacement product: It is believed by some experts that recombinant products (those which contain no blood products) may be more likely to cause inhibitors than products derived from blood.

Presence of other immune disorders: Patients with other immune disorders may be at a higher risk of developing an inhibitor.

Symptoms

Patients who have developed an inhibitor do not respond as well to standard treatment with factor replacement products as they did prior to the inhibitor. Some signs that an inhibitor has developed may include the following:

- A bleed is not controlled with the normal dose of factor replacement product.
- Normal treatment becomes less and less effective.
- Bleeding becomes more and more difficult to control.

Diagnosis

Patients who have developed symptoms indicating the possible presence of an inhibitor or who have an abnormal APTT (a test which measures how long it takes for blood to clot) during routine blood work may be given a specific test (called a Bethesda assay) to detect the presence of an inhibitor.

Inhibitor levels vary from patient to patient and can vary in the same person over time. The Bethesda assay gives a measurement of the amount of inhibitor present in the patient's blood at the time of the test. This is referred to as the number of Bethesda units (or BU). If a level is more than 5 BU, it is considered "high titer". Anything less than 5 BU is considered "low titer". Typically, high titer inhibitors work more quickly and completely to neutralize infused factor replacement products than low titer inhibitors, but this is not always true.

Treatment

Patients with inhibitors are more difficult to treat than other patients with hemophilia, and there are many approaches that can be taken. Hematologists who specialize in the treatment of bleeding disorders are the most qualified persons to help patients decide which is the most appropriate choice of therapy. Possible options for management of bleeding in patients who have an inhibitor include the following:

High Dose Factor Concentrates: Administering factor replacement products at higher doses and/or frequencies.

Bypassing Agents: These agents work by bypassing the factor to which there is an inhibitor in the clotting cascade. There are currently two FDA approved bypassing agents available in the US: NovoSeven RT (Recombinant Factor VIIa) and Feiba (APCC).

Plasmapheresis: A procedure which removes inhibitors from a patient's bloodstream. This is usually performed in instances where titers need to be brought down quickly (such as just before surgery or in cases of severe bleeding that is not responding to bypassing agents).

Immune Tolerance Induction Therapy (ITI): Involves giving a patient with inhibitors frequent doses of factor replacement products over several months, or even years, in order to train the body to recognize it without responding negatively to it.

** For further information or questions, please feel free to contact Family Factor at 251-633-8090 or Toll Free at 1-877-611-0004.*

REFERENCES:

1. World Federation of Hemophilia, "What are Inhibitors". 06/02/2011 http://www.wfh.org/2/docs/Publications/Inhibitors/Inhibitors_booklet_ENG.pdf
2. Center for Disease Control and Prevention, "Inhibitors". 06/02/2011 http://www.cdc.gov/ncbddd/hemophilia/inhibitors.html